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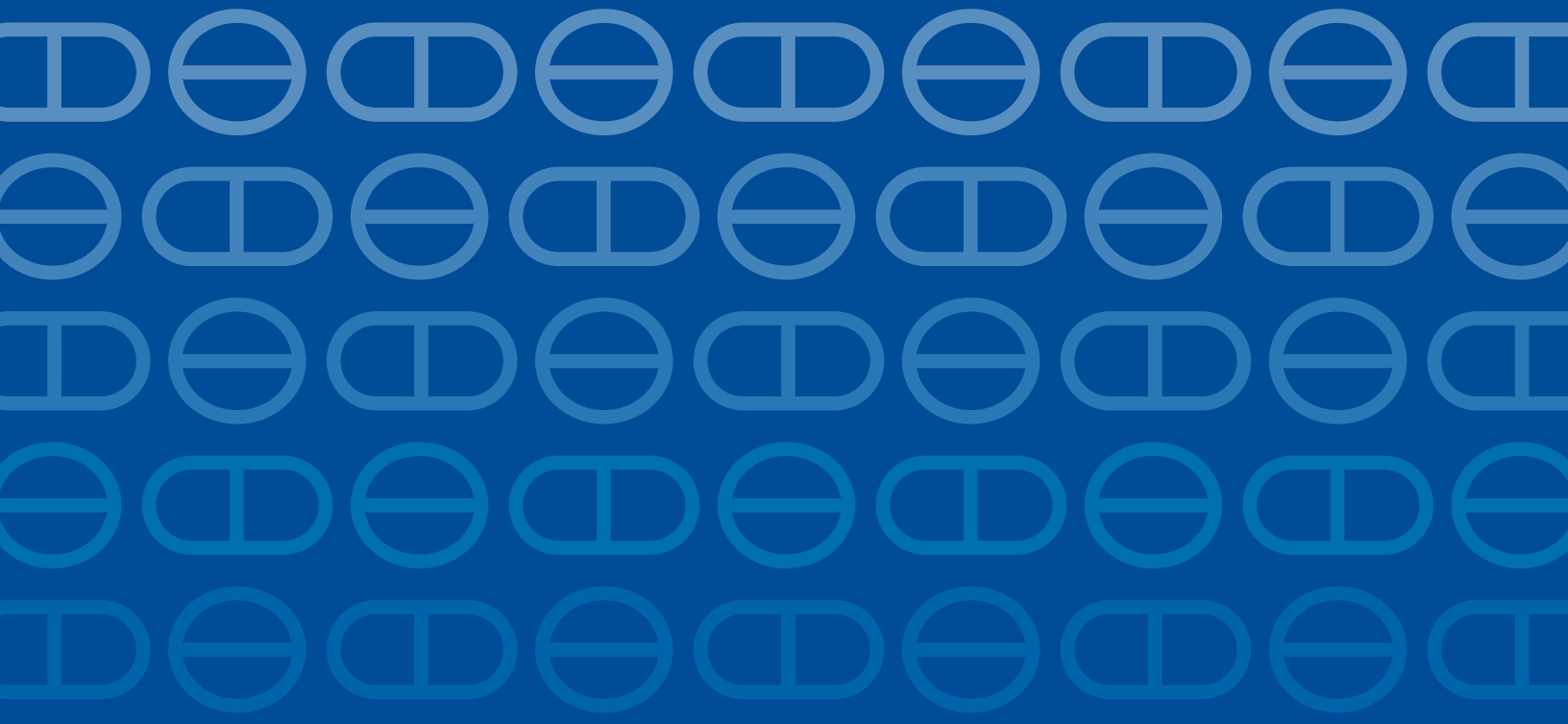
Are you PrEPared?

Evidence-based prevention of HIV infection in at risk individuals



Are you PrEPared?

Evidence-based prevention of HIV infection in at risk individuals

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Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 0.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Activity Overview:

The goal of this activity is to educate prescribers about the most recent guidelines for the use of pre-exposure prophylaxis (PrEP) for reducing the risk of acquiring human immunodeficiency virus (HIV). Evidence for the safety and efficacy of the currently available PrEP formulation (tenofovir plus emtricitabine) will be presented, along with the latest data on HIV epidemiology, risk groups, and HIV infection rates. Evidence-based recommendations will be made for identifying patients who might benefit from PrEP and for implementing an ongoing prevention program. In addition to providing this evidence report, the education program uses an innovative approach: academic detailing, which involves one-on-one educational sessions in physicians' offices with trained outreach educators (pharmacists, nurses, physicians) who present the educational material interactively. Reference cards for clinicians and education materials are also provided.

Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Describe the evidence supporting tenofovir/emtricitabine for pre-exposure prophylaxis (PrEP) for the prevention of HIV
- Identify patients at high risk for HIV infection who could potentially benefit from PrEP
- Prescribe PrEP to identified patients, educate patients about risk reduction, monitor adherence and ensure appropriate follow-up for patients on PrEP

Disclosure Policy:

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The following committee members from Harvard Medical School's Continuing Medical Education program also reviewed this educational activity: Gyorgy Baffy, MD, PhD, James Burns, MD, Laura Collins, MD, Harvey Katz, MD, Louis Pasquale, MD, John Sharp, MD, Jane Sillman, MD, J. Kevin Tucker, MD. Louis Pasquale, MD disclosed the following relationships: Bausch + Lomb: Paid consultant, Novartis: Non-paid consultant, Allergan: Speaker, NEI: Grant, Merck: Unrestricted Grant. All other committee members have no relevant financial relationships to disclose.

Media used:

Printed educational material.

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The activity will take approximately 0.75 hours to complete.

Activity publication date: April 1, 2017

Termination date: April 1, 2020

Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

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Introduction

Despite the expansion of screening and treatment programs, the human immunodeficiency virus (HIV) continues to spread. Many mechanisms to prevent the transmission of HIV, such as the development of a vaccine, have yet to prove successful. The quest for alternative prevention methods led to the use of antiretroviral medications to reduce the risk of HIV transmission, now considered pre-exposure prophylaxis (PrEP).

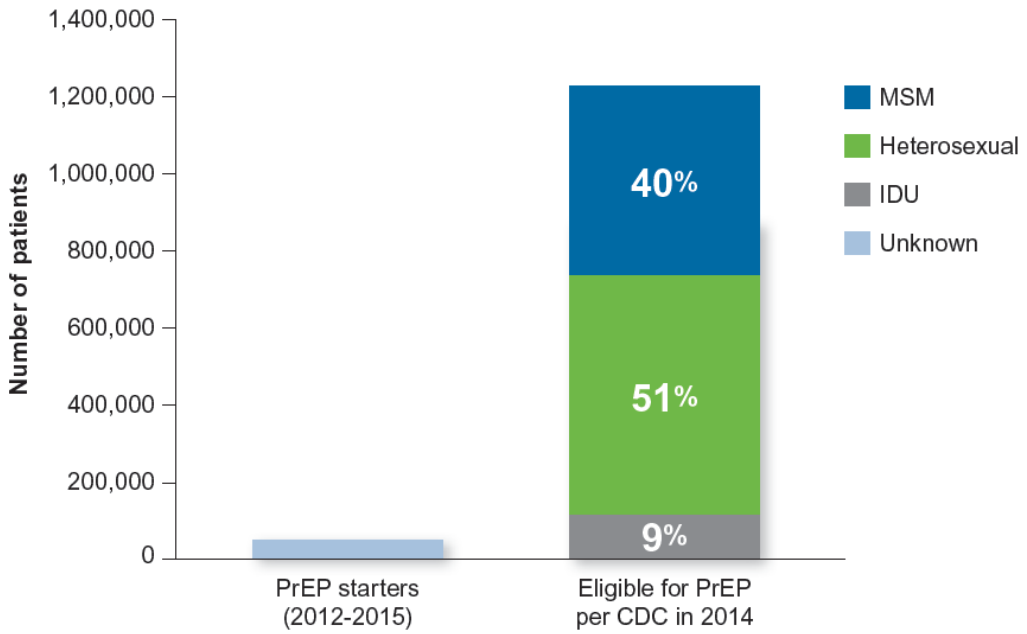
In recent years, some of the news about HIV has been encouraging. Overall, the number of new HIV diagnoses in the U.S. fell 19% from 2005 to 2014.[1] Thanks to improved antiretroviral (ARV) regimens, HIV infection can now be effectively managed and controlled.[2] Patients are living longer and HIV is now considered a chronic disease, like diabetes or heart disease.

Against this generally positive background, however, are continuing challenges. About 40,000 Americans became infected with HIV in 2015, the most recent year for which data are available, and about 1.2 million people in the U.S. are currently living with HIV.[3] Roughly one in every eight of these people (roughly 13%) don't know they are infected, because they have no symptoms and/or have never been tested.[1]

More alarmingly, the trends of HIV infection for some groups have actually risen. The diagnosis of HIV increased 22% between 2005 and 2014 among gay and bisexual African American men.[1] Among young African American and Latino gay and bisexual men (ages 13-24), the rise was 87%.[1] While the rate of HIV infection is lower in women, African American women account for a disproportionate number of new infections, over 60% of all cases in women.[3]

In July 2012 the U.S. Food and Drug Administration (FDA) approved the use of a once-daily pill that combines the ARVs tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) along with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk.[4] Findings from a number of clinical trials have demonstrated that this medication is relatively safe and can significantly lower the risk of acquiring HIV with consistent use.[5] And yet, even though the use of PrEP has risen significantly in recent years, most patients who are eligible for PrEP are not being treated (Figure 1, next page).[6,7]

Figure 1. Patients started on PrEP vs. those eligible for PrEP[6,7]



In addition, many primary care providers are not aware of PrEP or the protocols for its use. In a 2015 survey, 34% of primary care doctors and nurses had not heard of PrEP.[8]

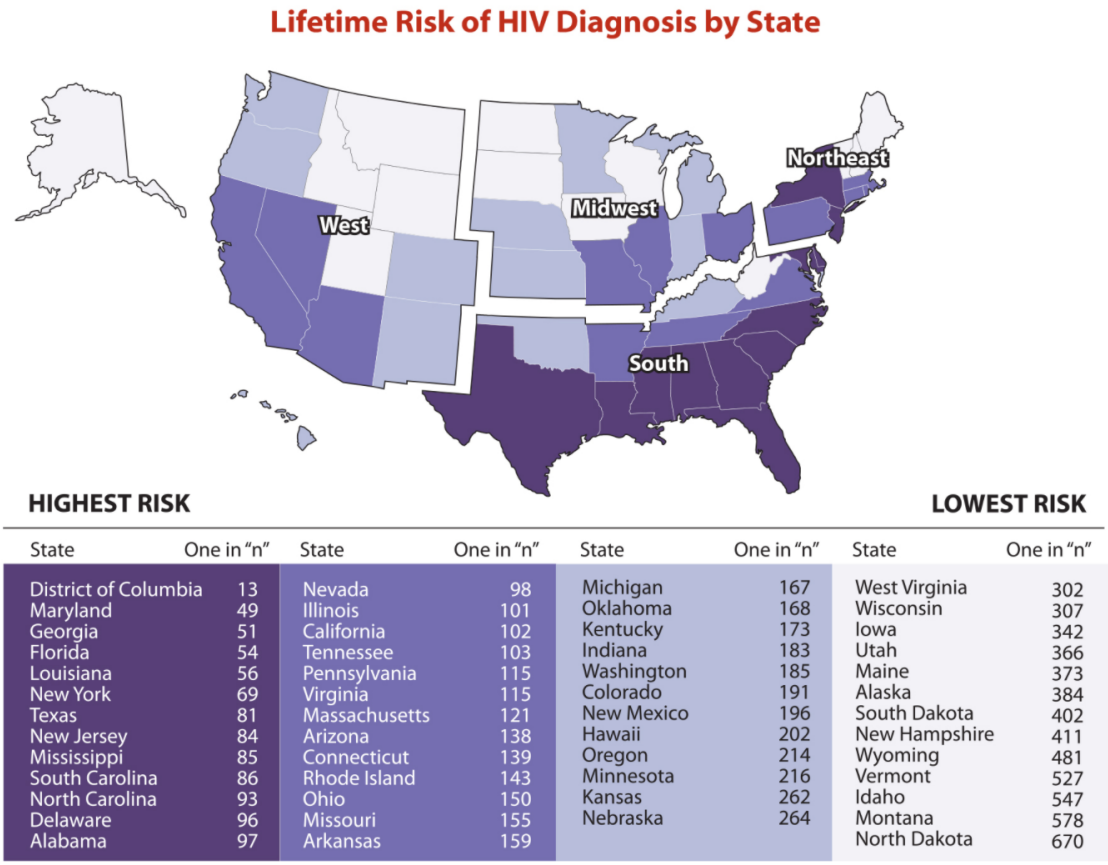
This monograph provides a summary of the evidence for the safety and efficacy of PrEP and practical guidance for identifying and treating patients who may benefit from this medication.

Other forms of PrEP exist (e.g., ring, vaginal gel, injectables) and have been tested in clinical trials, however only the previously-mentioned oral product has been approved by the FDA for this indication at the time of this writing.

Epidemiology

In the U.S., the lifetime risk of HIV infection varies widely by geography, with risk being the highest in the southeast and the lowest in northern New England and the north-central Midwest (Figure 2, next page).

Figure 2. Risk of HIV infection by state[9]



State	One in "n"	State	One in "n"	State	One in "n"	State	One in "n"
District of Columbia	13	Nevada	98	Michigan	167	West Virginia	302
Maryland	49	Illinois	101	Oklahoma	168	Wisconsin	307
Georgia	51	California	102	Kentucky	173	Iowa	342
Florida	54	Tennessee	103	Indiana	183	Utah	366
Louisiana	56	Pennsylvania	115	Washington	185	Maine	373
New York	69	Virginia	115	Colorado	191	Alaska	384
Texas	81	Massachusetts	121	New Mexico	196	South Dakota	402
New Jersey	84	Arizona	138	Hawaii	202	New Hampshire	411
Mississippi	85	Connecticut	139	Oregon	214	Wyoming	481
South Carolina	86	Rhode Island	143	Minnesota	216	Vermont	527
North Carolina	93	Ohio	150	Kansas	262	Idaho	547
Delaware	96	Missouri	155	Nebraska	264	Montana	578
Alabama	97	Arkansas	159			North Dakota	670

Source: Centers for Disease Control and Prevention

Risk also varies by race and gender. Overall rates of HIV infection in blacks are more than 2.5 times higher the rate in Hispanics/Latinos and more than 8 times higher than the rate in whites.[10]

Table 1. HIV infection rates by race/ethnicity in 2015[3]

Race/ethnicity	Number of infections	Rate of infection per 100,000
Black/African American	17,670	44.3
Hispanic/Latino	9,290	16.4
Native Hawaiian/other Pacific Islander	79	14.1
Multiple races	801	12.2
American Indian/Alaska Native	209	8.8
Asian	955	5.5
White	10,509	5.3
Total	**39,513**	**12.3**

The rate of new HIV infections for men, 24.4 per 100,000, is 4.5 times higher than the rate for women, with men who have sex with men (MSM) having the greatest risk of HIV infection, accounting for two-thirds of new HIV infections.[10] Women primarily contract HIV through

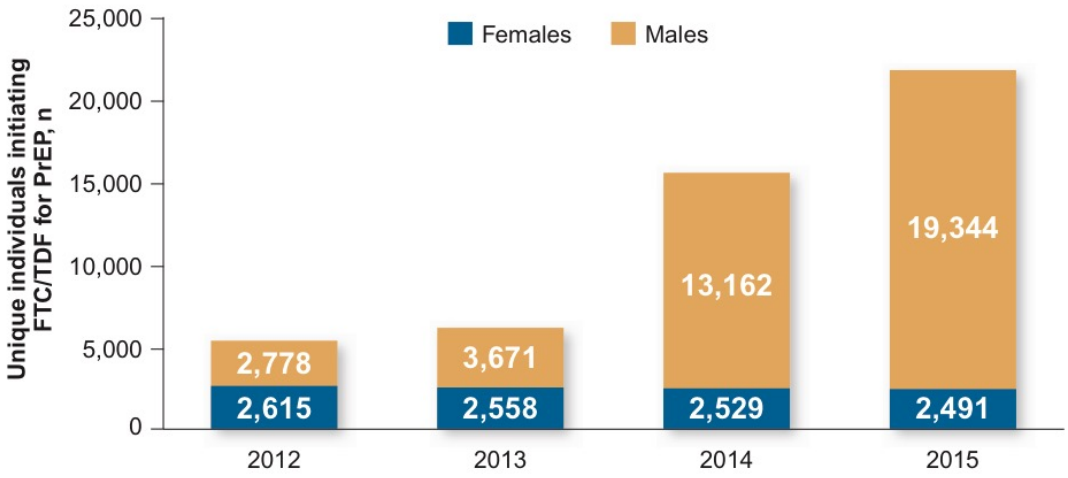
heterosexual contact, with the risk for a female partner twice that of the male partner.[11] The rate of new infections in women is 5.4 per 100,000. African American women, however, account for over 60% of all new infections in women.[10]

Despite national campaigns to educate the public about the dangers of HIV and the need to get tested, an estimated 1,242,000 persons age 13 and older are living with HIV infection, which includes an estimated 161,200 (13%) who do not know they are infected.[12] The percentage of young people (age 13-24) who are unaware of being infected is particularly high, 41%, and young people ages 20-29 had the highest rates of infection in 2015.[3] These individuals bear the risk of progressive HIV and AIDS and are also at high risk of unknowingly transmitting the infection to others.

PrEP use and opportunities

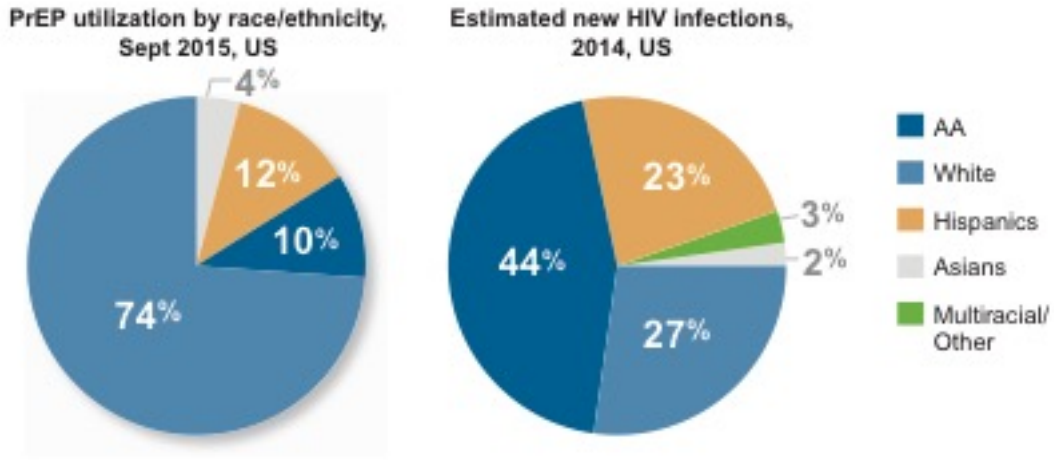
PrEP represents an opportunity to address the worrisome HIV trends just described, although the use of PrEP varies significantly across populations. For example, men are far more likely to initiate PrEP than women (Figure 3), even though women represent a large proportion of those at risk for HIV from heterosexual contact (Figure 1, page 2).

Figure 3. Use of PrEP by sex[6]



Racial disparities also exist in PrEP initiation, and the distribution of new diagnoses does not reflect the usage of PrEP. African Americans, who suffer the greatest burden of HIV, have a disproportionately low rate of PrEP use (Figure 4, next page). Health care providers should consider a population's risk of HIV infection when assessing the potential utility of PrEP.

Figure 4. Use of PrEP by race[6]



BOTTOM LINE: Although HIV infection rates overall have stabilized in recent years, rates have increased significantly in some sub-populations. PrEP has been approved since 2012, but its use is not widespread and many people eligible for PrEP are not being treated.

What is PrEP?

PrEP is the use of an antiretroviral medication to prevent HIV infection in someone who is not infected with HIV. PrEP is, therefore, taken *before* potential exposures (e.g., before sex or intravenous injection of drugs). PrEP should not be confused with post-exposure prophylaxis (PEP), which is the use of ARV medications *after* a potential exposure to reduce the risk of infection (see the section on PEP later in this monograph).

PrEP is just one part of a comprehensive HIV prevention strategy which should include educating patients about risk reduction techniques, use of condoms, use of clean needles for injecting drugs, and knowing the HIV status of any sexual partners.

The currently-approved medication for PrEP comes in one co-formulated strength: TDF 300mg/FTC 200 mg. The components are nucleoside/nucleotide analogues, which act as false substrates for reverse transcriptase, interfering with reverse transcription and thus preventing HIV replication.[13] TDF-FTC is not effective alone for the treatment of established HIV infection, but is used with other ARVs in treatment regimens.

Evidence for efficacy

PrEP has been studied in a variety of sub-populations:

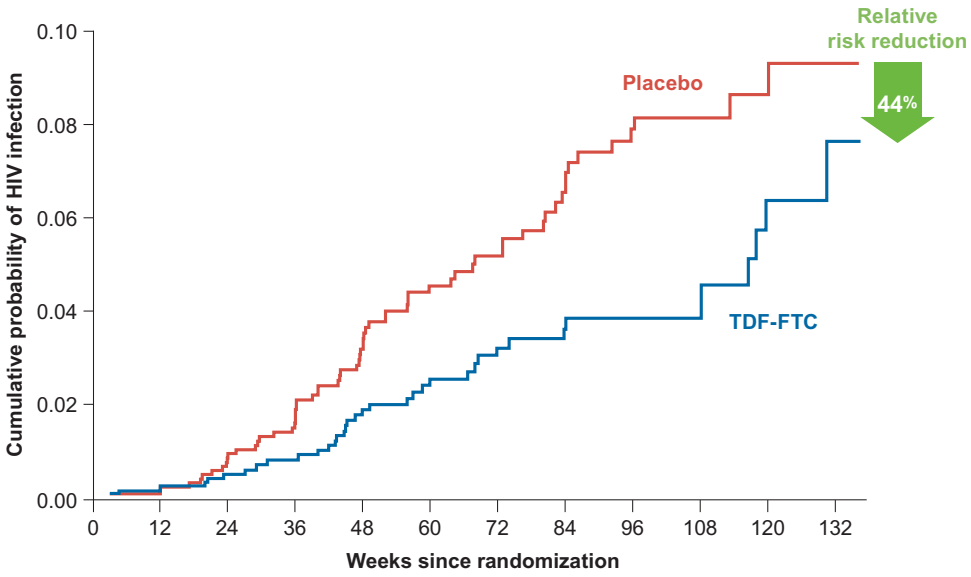
- men who have sex with men [MSM] and transgender women,

- serodiscordant couples,
- injection drug users, and
- heterosexual women

iPrEx: MSM and transgender women

The Global iPrEx study was one of the largest early studies of PrEP with 2499 HIV-negative men who have sex with men or transgender women in the U.S., South America, Africa, and Thailand randomized to either daily TDF-FTC (300 mg/200 mg) or placebo.[14] All subjects received sexually transmitted infection (STI) screening, risk-reduction counseling, and condoms at each study visit. Both arms of the study were well-matched for risk factors such as age, number of sex partners, and percentages of subjects who had unprotected receptive anal intercourse (the highest risk sexual behavior) in the past 12 weeks. After a median follow-up of 1.2 years, 100 subjects became infected, 36 in the treatment group vs. 64 in the control group, indicating a 44% relative risk reduction (RRR) with use of TDF-FTC (NNT = 36).[14] Although participant-reported pill use in the study was high, drug exposure that was measured using drug levels was substantially lower, suggesting low adherence rates. In a prespecified subanalysis that measured drug levels among subjects who acquired HIV infection and matched controls who remained HIV seronegative those with detectable drug levels (suggesting adherence) had a 92% lower risk of transmission.

Figure 5. Results from Global IPrEx study, 2010[14]



Partners PrEP: serodiscordant couples

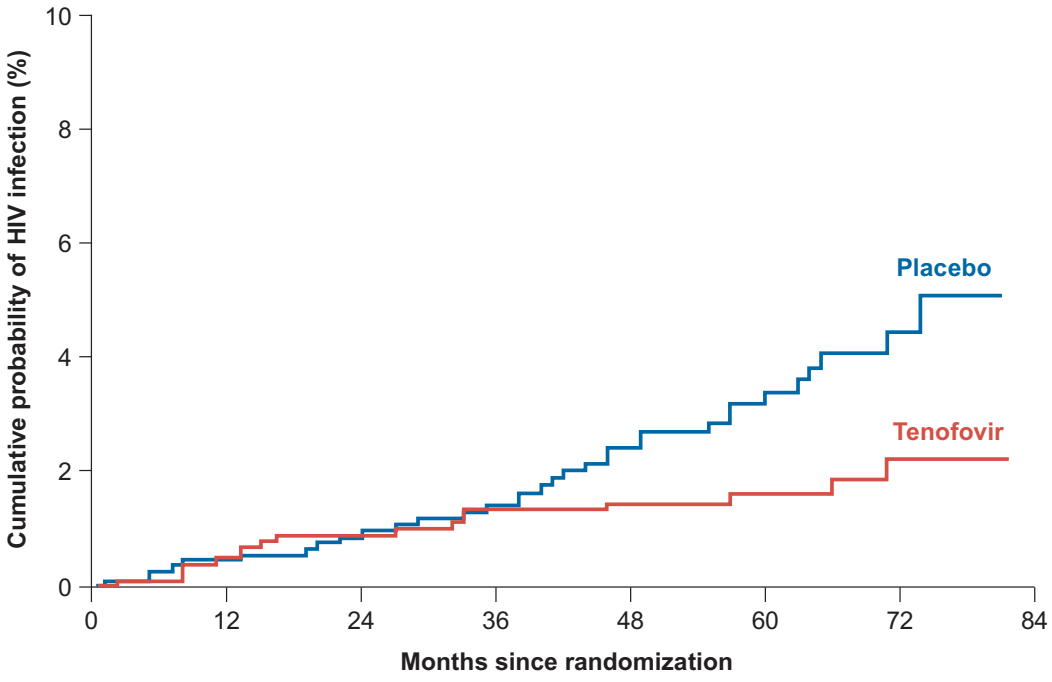
The Partners PrEP study enrolled 4758 HIV serodiscordant couples (i.e., one person of the couple is HIV positive while the other is HIV negative) in Uganda and Kenya. HIV positive partners were not currently receiving treatment for HIV. Each HIV negative partner was assigned to one of three arms: TDF-FTC (300 mg/200 mg), TDF only (300 mg), or placebo.[15] After a median follow-up of 1.9 years subjects on TDF alone had a 67% reduction in RRR of acquiring HIV compared to those on placebo, and those on TDF-FTC had an RRR of 75%.[15] Adherence to study medication was 92% based on pill counts and medication dispensations. A sub-analysis of

blood samples from 198 participants was used to assess adherence; the risk of transmission among individuals with detectable levels of TDF-FTC was lowered by 90% compared with individuals who had undetected levels.

BTS: injection drug users

The Bangkok Tenofovir Study (BTS) was a randomized, placebo-controlled trial of 2413 injection drug users in Bangkok, Thailand randomly assigned to either daily tenofovir (300 mg) or placebo.[16] In addition to TDF, patients were offered risk-reduction counseling (e.g., education to reduce needle sharing), methadone treatment, condoms and bleach to clean injection equipment. Adherence rates in both study arms was 83.8%.[16] After a mean follow-up of 4 years, there were 35 cases of HIV in the placebo group vs. 17 in the TDF group for a 48.9% relative reduction in HIV incidence (95% CI: 9.6-72.2; p=0.01).[16]

Figure 6. Bangkok Tenofovir Study: Tenofovir 300 mg daily vs. placebo[16]



Although this study was not conducted using TDF-FTC, the demonstrated reduction in HIV from TDF alone suggests that PrEP may provide effective prevention for injection drug users.

Heterosexual women: FEM-PrEP, VOICE and the importance of adherence

Two studies of PrEP in women had equivocal results. The FEM-PrEP study randomized 2120 women with increased risk of HIV in South Africa, Kenya, Tanzania to TDF-FTC or placebo.[17] The trial was stopped early for futility. Adherence as measured by drug plasma levels was low (<30%), and 18% of study subjects dropped out. HIV infections were not significantly reduced in either study group (HR 0.94; 95% CI: 0.59-1.52).[17] In the VOICE trial, 5029 heterosexual women from sub-Saharan Africa were randomized to oral TDF-FTC, oral TDF, tenofovir vaginal gel (TFV), oral placebo or vaginal gel placebo.[18] Adherence to study drugs was low: 30%, 29%, and

25% of those assigned to TDF, TDF-FTC, and TFV, respectively, based on blood samples, while self-reported adherence was 90%.[18] Oral TDF and TFV were stopped early for futility. None of the drug regimens reduced the rates of HIV infection.[18]

Unfortunately, the results from FEM-PrEP and VOICE shed little light on the potential efficacy of TDF-FTC in women due to low adherence. The reasons for low adherence in these studies are not entirely clear, although women in FEM-PrEP and VOICE were younger (mean ages 24 and 25 respectively) than the other studies described above and may not have perceived themselves to be at high risk for HIV. In the Partners PREP study women who were in serodiscordant relationships and who knew they were at high risk had high levels of adherence and this trial showed greater efficacy in a subset of women only: 66% reduction from TDF-FTC and 71% reduction from TDF.[19] The results of the Partners PrEP study suggest that adherence, and not biological sex, is the key determinant of efficacy for PrEP.

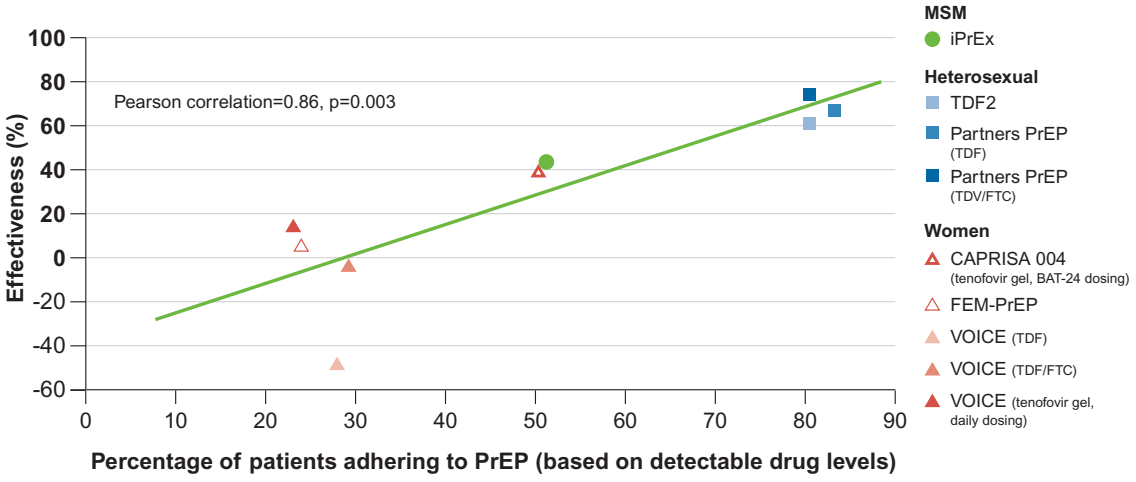
Real world application of PrEP

In studies of patients cared for in typical practice, rather than participants in clinical trials, PrEP also appears to be highly effective. For example, a 2015 Kaiser observational study of U.S. MSM tracked 657 people who initiated PrEP for 388 person-years of use (mean duration of use 7.2 months).[20] The mean age of the study group was 37 years, with 99% being MSM (there were 3 heterosexual woman and 1 transgender man in the group). There were no HIV diagnoses in any subjects during the study period.[20]

These and other studies of the TDF-FTC regimen clearly show that efficacy is correlated with adherence: PrEP works if you take it. Figure 7, shows the positive linear relationship between the percentage of patients adhering to PrEP in several studies and the effectiveness of PrEP in preventing HIV.

Studies of the TDF-FTC regimen clearly show that efficacy is correlated with adherence: PrEP works if you take it.

Figure 7. Effectiveness and adherence in trials of oral and topical tenofovir-based regimens[21]



IPERGAY: the role of on-demand PrEP for MSM

Whether the TDF-FTC regimen can be used as an "on-demand" medication is the subject of a 2015 study by Molina et al. Four hundred MSM at high risk of HIV in France and Canada were randomized to TDF-FTC or placebo. Subjects were instructed to use the pills in a dosing schedule based on sexual activity (i.e., 2 pills 2-24 hours prior to sex, then 1 pill daily for 2 days after.[22] Other patterns of administration were used when sexual activity extended beyond a single encounter. After a median follow-up of 9.3 months, there were 2 HIV infections in the TDF-FTC group compared with 14 in the placebo group (RRR 86%; 95% CI: 40-98; p=0.002).[22] These results must be interpreted cautiously, however, because subjects took a median of 15 tablets per month (or approximately 4 tablets per week), effectively taking PrEP medication most days of the week.[22] PrEP used less frequently may not yield the same results.

In light of study results showing that a daily regimen of an oral medication for pre-exposure prophylaxis is challenging for many people, non-pill and longer-acting PrEP formulations are in development, such as a vaginal ring using the ARV dapivirine,[23] or a long-acting injection of the ARV cabotegravir.[24] At present, however, the CDC recommends continuous daily use of oral PrEP using the TDF-FTC regimen.[5]

BOTTOM LINE: Daily use of TDF-FTC can significantly reduce the risk of HIV among high risk groups.

Safety

In clinical trials of TDF-FTC, rates of symptomatic side effects have been similar between control and treatment arms (Table 2), and tend to be relatively mild and limited to dizziness, nausea/vomiting, and weight loss.[5] Other side effects include a decline in renal function and bone mineral density.

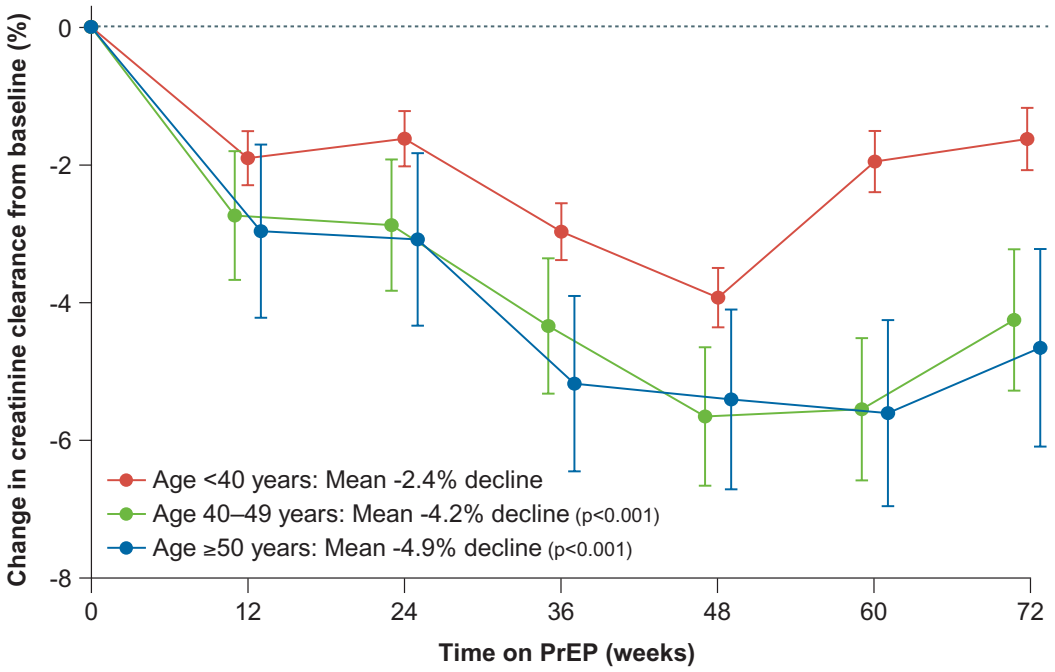
Table 2. Safety differences between TDF-FTC and placebo from selected studies[14-16]

Study	Side effect	No. of events (TDF-FTC vs. placebo)	P-value
iPrEx	Nausea Decreased weight	22 vs. 10 34 vs. 19	0.04 0.04
Partners PrEP	Diarrhea	571 vs. 474	0.03
BTS	Nausea/vomiting Elevated ALT (grade 1 or 2)	96 (8%) vs. 59 (5%)* 635 (53%) vs. 587 (49%)*	0.002 0.003

* side effects are for TDF alone

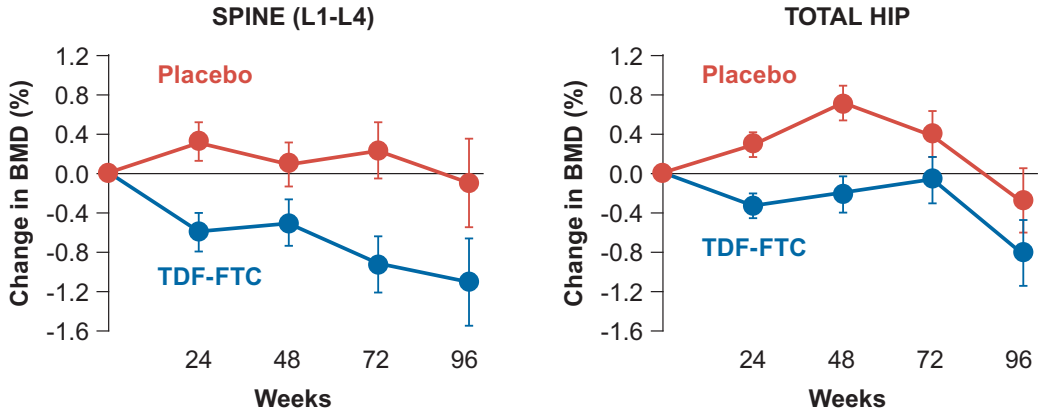
Studies show that renal function typically declines 3-5% from baseline among patients on TDF-FTC.[25] A longer duration of TDF use is associated with a greater decline in renal function as is older age and lower baseline renal function.[25] PrEP is, therefore, not recommended in patients with baseline creatinine clearance <60mL/min. In one trial (iPrEX), renal function returned to normal after TDF-FTC was discontinued.[25]

Figure 8. Change in creatinine clearance over time for iPrEx OLE participants by baseline age.[25]



Some patients on TDF-FTC have experienced modest bone mineral density loss compared to patients on placebo (i.e., reductions of 1%-3% on DEXA scans).[26] These reductions were not associated with an increased rate of fractures, and bone density generally recovers after stopping PrEP.[26]

Figure 9. Changes in bone mineral density during treatment with PrEP[26]



In most clinical trials, patients with hepatitis B infection were excluded because of TDF-FTC's activity against hepatitis B. However, patients with hepatitis B can receive TDF-FTC in consultation with their hepatologist or infectious disease provider.

HIV resistance

Drug resistance is a significant issue in HIV prevention and treatment because roughly 10% of newly-acquired HIV cases demonstrate some degree of resistance.[5,27] In the studies cited above (excluding VOICE and FEM-PrEP because of their very low adherence rates) none of the subjects who seroconverted had HIV strains resistant to TDF and FTC.[5] To date, only one case report of drug resistant HIV has emerged among PrEP treated patients, and may not reflect resistance acquired from exposure to PrEP. Knox et al, report a case of a 43-year-old man adherent to PrEP for 2 years who became infected with HIV.[28] Genotyping of the virus revealed that it was resistant not only to TDF-FTC, but to other ARV classes as well. Since the patient's drug levels suggest he was adherent at the time of infection, this case probably reflects transmission of a resistant strain.

BOTTOM LINE: TDF-FTC PrEP is generally well tolerated. Few participants in relevant clinical trials discontinued study drugs due to serious adverse events. Since TDF is active against hepatitis B, patients should be screened prior to starting PrEP.

Potential barriers to PrEP prescribing

One challenge of providing patients with an effective treatment plan for PrEP has been called the "purview paradox": it has not been clear which providers are best positioned to provide this preventive service to their patients. The strengths of the various types of care providers are in some ways offset by aspects of the nature of the care that they typically provide (Table 3).[29]

Table 3. The "purview paradox"[29]

Provider	Strengths	Limitations
Primary care providers	Strong longitudinal relationships and follow-up	Not familiar with prescribing ARVs
STI clinics	Provide HIV testing, STI screening and treatment, sexual health promotion	Episodic care with inconsistent follow-up
HIV providers / Infectious disease specialists	Most experience managing ARVs	Limited number of HIV negative patients

Some barriers to prescribing PrEP may be less significant that some PCPs believe. A survey by Krakower et al., of "early adopter" prescribers of PrEP suggests that although financial barriers were significant, rates of patient non-adherence and toxicity were low (Table 4).[30] Financial concerns may be less relevant now due to the fact that health insurance plans, both public and private, are increasingly providing coverage for oral PrEP.

Table 4. Lessons from early PrEP prescribers[30]

Barrier (perceived or actual)	Percent (n=31)
Patient lacked insurance coverage	48%
Fair or poor adherence	0%
Reason for discontinuation Patient preference Intolerant to medication Laboratory abnormalities Cost	 58% 19% 13% 20%
PrEP challenging or very challenging to prescribe	6%

To specifically address the unfamiliarity of this type of prevention for some primary care physicians (PCPs), some have advocated a "reframing" education effort for PCP's in which the clinical logic and implementation logistics of PrEP are compared with those involved in the prescription of oral contraceptives (Table 5).

Table 5. Reframing PrEP as similar to oral contraceptive

Characteristic	PrEP	Oral contraceptive pill (OCP)
Population	MSM, high-risk heterosexual sex, injection drug use	Women of reproductive age
Directions	1 tablet daily	1 tablet daily (most common)
Effectiveness when adherence is high	+++	+++
Safety concerns	Acute kidney injury, decreases in bone mineral density	Blood clots
"Ethical" concerns	Increased sexual risk taking	Increased sexual risk taking

Recommendations for initiating PrEP

Comprehensive recommendations for implementing PrEP services have been provided by the CDC and local departments of health. Visit AlosaHealth.org/modules/PrEP for links to these and other guidelines.

Prescribe PrEP using five steps:

1. Assess HIV risk
2. Check labs
3. Ensure patient access to medication
4. Prescribe PrEP
5. Follow up

Assessing patient's risk of HIV

A sexual health history is central to understanding a patient's risk for HIV. "The Five P's" can guide the key components of a comprehensive sexual health history: Partners, Pregnancy, Protection from STIs, Practices, Past history of STIs.

Table 6. Components to a sexual health history

The Five P's	
Partners	• Understand who and how many people the patient has had sexual contact with • Ask about relationships and the HIV status of partners • Example questions: Do you have sex with men, women, or both? Are any of your partners HIV positive?
Practices	• Have the patient describe their sexual contact with others, what type of contact they engage in and what protection they use • Example questions: Do you use condoms other types of protection? If not, why not? • Have you ever had sex in exchange for something you needed (e.g., food, shelter, money)?
Protection from STIs	• Inquire about their perceived concern regarding contracting an STI or HIV
Past history of STIs	• Understand if the patient or their partner(s) have been treated for STIs in the past
Pregnancy	• Ask about a patient's goals regarding pregnancy

See Appendix 1 for a full list of questions for each of the 5 Ps.

The question about transactional (e.g., for food, shelter) or commercial sex can help a clinician explore the extent to which patients have control over their choice of sexual partners. Reduced control of choice increases the risk of contracting HIV.[31]

Transgender populations are also vulnerable to HIV infection; discussing sexual practices and preferences in this patient population may be unfamiliar for some providers. When taking a sexual history with a transgendered patient, ask by which name and gender they prefer to be called, how they refer to different parts of their body, and remember that gender and choice of sexual partners are different. If you are unfamiliar with any terminology used, ask for clarification.

Several factors increase a patient's risk for HIV infection and may, therefore, help identify candidates for PrEP (Table 7).

Table 7. Patient characteristics suggesting HIV risk[5]

Strong indication for PrEP	Action
Sexual or injecting partner with HIV	Offer PrEP
Commercial sex work	
High number of sex partners	
Possible indication for PrEP	
Recent bacterial STI	Discuss the person's risk and preferences to determine if PrEP is the right course.
Lives in high-prevalence area or network	
Sharing injection equipment	
Recent relapse of injection drug use	

As in clinical trials, risk reduction strategies such as condom or other barrier protection use, knowing a partner's HIV status, and participating in treatment programs and/or clean needle programs for injection drug users, should be discussed as part of a comprehensive strategy to prevent HIV infection.

Laboratory screening

The following tests are recommended for any patient considering PrEP.

- HIV
- renal function
- hepatitis B serologies
- pregnancy status, in women

HIV testing. Patients initiating PrEP must be HIV negative and cannot have signs or symptoms of acute HIV infection (e.g., fever, rash, sore throat, cough, lymphadenopathy). When available, 4th generation tests are recommended because they look for both HIV antibodies and antigen and may detect recent HIV infection (2-6 weeks after exposure).

Renal function. Because of the potential risks for reduced renal function reviewed earlier, patients initiated on PrEP should not have a creatinine clearance <60 mL/min. In rare cases acute renal failure or Fanconi syndrome may occur.[13]

Hepatitis B serologies. A potential benefit of PrEP is that TDF is active against hepatitis B.[13] This means that hepatitis B status should be established before starting PrEP as hepatitis B would be an independent indication to continue treatment even if PrEP is not longer necessary to prevent HIV infection. In patients who have unknown hepatitis B status, hepatitis serologies should be obtained:[32]

- Hepatitis B surface antigen (HBsAg),
- Heaptitis B surface antibody (anti-HBs),
- Total hepatitis B Core antibody (anti-HBc), and
- IgM antibody to hepatitis B core antigen (IgM anti-HBc)

The table on the next page outlines the steps to be taken relative to PrEP initiation based on hepatitis B status.

Table 8. Interpretation of hepatitis B serologic test results[32]

Tests	Results	Interpretation	OK to start PrEP
HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible	Yes, and vaccinate
HBsAg anti-HBc anti-HBs	negative positive positive	Immune due to natural infection	Yes
HBsAg anti-HBc anti-HBs	negative negative positive	Immune due to hepatitis B vaccination	Yes
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	Acutely infected	Re-evaluate, after acute infection addressed
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	Chronically infected	Yes, after conversation with specialist
HBsAg anti-HBc anti-HBs	negative positive negative	Interpretation unclear: 1. resolved infection 2. false positive anti-HBc, thus susceptible 3. 'low level' chronic infection 4. resolving acute infection	

Patients with hepatitis B should be counseled to speak with their primary care provider or specialist prior to discontinuing TDF-FTC, since removing PrEP without providing alternative treatment may result in clinically significant rebound hepatitis.[13] The patient's specialist may help guide hepatitis treatment upon PrEP discontinuation. For more detailed information regarding hepatitis B serologies, vaccination and treatment, please visit AlosaHealth.org/modules/PrEP for links to CDC guidelines and other materials.

PrEP and pregnancy: Women without HIV infection who have unprotected sex with partners with documented HIV infection are at substantial risk of HIV acquisition.[5] In addition, pregnancy is associated with an increased risk of HIV acquisition.[37] PrEP use periconception and during pregnancy by the uninfected partner may offer an additional tool to reduce the risk of sexual HIV acquisition. Both the FDA labeling information and the perinatal antiretroviral treatment guidelines permit this use.[38] However, data directly related to the safety of PrEP use for a developing fetus are limited. A single small study of periconception use of TDF in 46 uninfected women in HIV-discordant couples found no ill effects on the pregnancy and no HIV infections.[39] The data on pregnancy outcomes in the Antiretroviral Pregnancy Registry provide no evidence of adverse effects among fetuses exposed to these medications.[40]

BOTTOM LINE: PrEP should never be started in patients who have HIV infection. Renal function should be normal. Hepatitis B is not a contraindication for PrEP, but in patients with hepatitis B infection make a plan to manage it before starting TDF-FTC. PrEP can be used before or during pregnancy to reduce the risk of HIV infection. Providers should

discuss potential risks and benefits of beginning or continuing PrEP during pregnancy so that an informed decision can be made.

Access to treatment and follow-up

Understanding a patient's ability to pay for medication and connecting them to the needed resources is a critical component of PrEP services. As noted previously, the cost of PrEP can be a barrier to treatment. Some, but not all, insurance plans cover the medication for PrEP, as well as clinical visits and laboratory tests, although prior authorization may be required.

For patients without insurance or who have insurance that does not cover oral PrEP: The manufacturer of TDF-FTC, Gilead Sciences, has a patient assistance program that may cover the entire costs of the medication for persons without insurance and for persons with insurance, it may cover some co-pays and deductibles (start.truvada.com). Additionally, if the patient lives in a state with expanded Medicaid, Gilead may help cover the costs of medication while a patient's Medicaid application is pending. To qualify for the program, patients must reside full time in the United States, have a valid prescription, and must not exceed income thresholds (500% of the Federal Poverty Level or $59,400 for a single individual). While Gilead may help pay for medications, the company generally does not cover the costs of clinic visits or laboratory tests. Consider referring these patients to federally qualified health centers or clinics that accept payment based on a sliding scale.

For patients with commercial insurance, but who still have difficulty affording the medication (e.g., high co-pays), Gilead has a copay assistance card (gileadadvancingaccess.com, visit copay support). The program covers up to $3,600 in co-pays per year with no monthly limit. Note: patients with Medicare Part D or Medicaid are (by law) excluded from this program. These patients may receive some help through charity copay assistance programs such as the Patient Access Network Foundation (panfoundation.org) or other local or regional programs may cover some medication costs for selected patients.

Prescribe PrEP

Patients should fully understand the potential risks and benefits of PrEP as well as the importance of strict adherence to the one-tablet-per-day regimen (initial prescriptions are typically for 30 days). PrEP is most effective for patients who adhere to therapy; over 90% infections can be prevented if PrEP is taken daily. However, patients should know that PrEP is not 100% effective and that, therefore, other risk reduction strategies (e.g., condoms, clean needles) are advisable. Side effects should be described, noting that headache and nausea typically resolve within the first month, and that other side effects are generally reversible upon discontinuation.

Follow-up

The recommended schedule for follow-up tests for a patient on PrEP:

- every 3 months: HIV test
- every 6 months: renal function; STIs

Prescriptions at follow-up should not be written for longer than 90 days, and clinicians should continue to reinforce messages about safe sex and the importance of adherence at every visit.

Stopping PrEP

Some patients will no longer require PrEP after a change in their level of risk – e.g., the end of a serodiscordant relationship, cessation of IV drug use, or start of a monogamous relationship with a known negative partner. These changes should be evaluated at follow up visits. At present, intermittent use of PrEP is not recommended, although studies of this use pattern are ongoing.[33] Such use patterns are suggested by studies that show distinct "seasons of risk" among men who have sex with men. For example, of 7300 MSM respondents who had vacationed in the past year, 25% reported unprotected anal sex with new male sex partners while vacationing.[34] In this same survey, 93% of respondents said that having to use PrEP every day was a barrier to use, although 74% said they would take PrEP if they knew it would be helpful for short periods of anticipated increased risk.[34] New data may emerge regarding alternative approaches, but at present, continuous PrEP is recommended.[5]

BOTTOM LINE: To initiate a PrEP regimen, assess patient risk; check labs; ensure patient access to medication; prescribe PrEP (counseling the patient about the need for strict adherence); follow up on recommended schedule.

Post-Exposure Prophylaxis (PEP)

Some patients may not be interested in or prepared for the daily medication regimen comprising PrEP. Another prevention option is Post-Exposure Prophylaxis or PEP.

Table 9. Comparison of PrEP and PEP

	PrEP	PEP
Objective	Prevent HIV infection BEFORE potential exposures	Prevent HIV infection AFTER known exposures
ARV class	Single	Dual or triple therapy
Duration	Months to years	4 weeks

PEP has been shown to reduce the risk of HIV infection by 81%.[35,36] PEP is a valid HIV prevention course for a person who experiences an isolated incident of sexual or injection-related HIV exposure. PEP is effective within 72 hours of the exposure.[36] The patient receives a 28-day regimen of antiretroviral medications based on the level of exposure. Patients who have completed PEP for non-occupational exposure should be offered PrEP if they have ongoing risk.

BOTTOM LINE: PEP is not recommended as a routine alternative to PrEP but it is a valid option for reducing the risk of HIV infection in patients who experience an isolated incident of sexual or injection-related exposure. Clinical visits related to a regimen of PEP may provide an opportunity for recommending PrEP.

Putting it all together

Despite much progress in reducing the overall infection rates from HIV, infection rates for some sub-populations are rising. PrEP is a potentially powerful means of halting the spread of HIV. Although PrEP is effective and safe, many eligible patients are not being treated and many opportunities to increase use exist.

When initiating patients on PrEP:

- Take a full sexual history to ascertain patient risk and determine PrEP eligibility.
- Screen labs: HIV, Hep B, renal function
- Counsel on PrEP and risk reduction.
- Establish a follow-up schedule.
- Use PrEP daily while studies for other dosing strategies are ongoing.

Appendix 1. Comprehensive questions for a sexual health history

- Partners
  - How would you describe the gender(s) of people you have sexual contact with?
  - In the past 2 months, with how many partners have you had sex?
  - Is it possible that any of your sex partners in the past year had sex with someone else while they were still in a sexual relationship with you?
  - Do you know the HIV status of your partner(s)?
- Pregnancy
  - What are your plans regarding pregnancy?
  - What (if anything) are you doing to prevent pregnancy?
- Protection from STIs
  - Are you concerned about getting an STI?
  - How do you protect yourself from STIs and HIV?
- Practices
  - Can you describe the type of sex you have with your partners?
  - Do you use condoms, dental dams, rubber gloves or other types of protection? If not, why not? If sometimes, in what situations do you use protection?
  - Have you ever had sex in exchange for something you needed (e.g., food, shelter, money)?
  - Is there anything else I should know about your sexual practices?
- Past history of STIs
  - Have you ever had an STI?
  - Have any of your partners had STIs?

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About this publication

These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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